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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,443	XIE ET AL.	
	Examiner	Art Unit	
	STEPHANIE K. MUMMERT	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 18-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 18-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 8, 2009 has been entered.

Applicant's amendment filed on January 8, 2009 is acknowledged and has been entered. Claims 1 and 32 have been amended. Claims 14-17, 30-36 have been canceled. Claims 1-13, 18-29 are pending.

Claims 1-13 and 18-29 are discussed in this Office action.

All of the amendments and arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This action is made NON-FINAL.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 6-9, 12-13, 18, 20-25 and 28 are rejected under 35 U.S.C. 103(a) as being obvious over Dauer et al. (Biotechnology and Bioengineering, 1991, vol. 37, p. 1021-1028) in view of Grevelding et al. (Nucleic Acids Research, 1996, 24(20), p. 4100-4101). Dauer teaches a method of isolating cells using magnetic particles (Abstract).

With regard to claim 1, Dauer teaches a process for amplifying a nucleic acid of a target cell or virus, which process comprises:

a) contacting a sample containing or suspected of containing a target cell or virus with a magnetic microbead not comprising a biomolecule that binds to said target cell or virus with high specificity (p. 1024, col. 2, where baker's yeast were the target cells and where the magnetic microbead comprises a magnetic "seed" comprising ferromagnetic gamma-iron oxide or maghemite (Fe2O3); see Table 1);

b) allowing said target cell or virus, if present in said sample, to bind to said magnetic microbead to form a conjugate between said target cell or virus and said magnetic microbead (Figure 6, where the process of mixing, binding and separation are depicted; p. 1025, col. 2, where the magnetic particles and the yeast are incubated together for 10 minutes, and where the

pH is used to control binding to the particles and then release of the particles);

c) separating said conjugate from other undesirable constituents via a magnetic force to isolate said target cell or virus from said sample (Figure 6, E, where the conjugate between the magnetic particle and the cells are separated from the sample),

wherein said biomolecule is selected from the group consisting of an antibody, an amino acid, a peptide, a protein, a nucleoside, a nucleotide, an oligonucleotide, a nucleic acid, a vitamin, a monosaccharide, an oligosaccharide, a carbohydrate, a lipid and a complex thereof (Table 1, p. 1024, col. 2, where the magnetic particle is not coated with a biomolecule or other affinity group).

With regard to claim 4, Dauer teaches an embodiment of claim 1, wherein the target cell is selected from the group consisting of an animal cell, a plant cell, a fungus cell, a bacterium cell, a recombinant cell and a cultured cell (p. 1024, col. 2, where baker's yeast were the target cells).

With regard to claim 6, Dauer teaches an embodiment of claim 1, wherein the magnetic microbead comprises a magnetizable substance selected from the group consisting of a paramagnetic substance, a ferromagnetic substance and a ferrimagentic substance (p. 1024, col. 2, where the magnetic microbead comprises a magnetic "seed" comprising ferromagnetic gamma-iron oxide or maghemite (Fe2O3); see Table 1).

With regard to claim 7, Dauer teaches an embodiment of claim 6, wherein the magnetizable substance comprises a metal composition (p. 1024, col. 2, where baker's yeast were the target cells and where the magnetic microbead comprises a magnetic "seed" comprising ferromagnetic gamma-iron oxide or maghemite (Fe2O3); see Table 1).

With regard to claim 8, Dauer teaches an embodiment of claim 7, wherein the metal composition is a transition metal composition or an alloy thereof (p. 1024, col. 2, where the magnetic microbead comprises a magnetic "seed" comprising ferromagnetic gamma-iron oxide or maghemite (Fe2O3); see Table 1).

With regard to claim 9, Dauer teaches an embodiment of claim 8, wherein the transition metal is selected from the group consisting of iron, nickel, copper, cobalt, manganese, tantalum, zirconium and cobalt- tantalum-zirconium (CoTaZr) alloy (p. 1024, col. 2, where the magnetic microbead comprises a magnetic "seed" comprising ferromagnetic gamma-iron oxide or maghemite (Fe2O3); see Table 1).

With regard to claim 12-13, Dauer teaches an embodiment of claim 1, wherein the magnetic microbead is untreated or modified with an organic molecule such as hydroxyl, carboxyl or epoxy (Table 1, p. 1024, col. 2, where the magnetic particle is not coated with a biomolecule or other affinity group).

With regard to claim 18, Dauer teaches an embodiment of claim 1, which further comprises washing the separated conjugate to remove the undesirable constituents before applying separated conjugate to a nucleic acid amplification system (p. 1021, col. 2, where the cells are washed with water and air).

With regard to claim 20, Dauer teaches an embodiment of claim 1, which is completed within a time ranging from about 0.5 minute to about 30 minutes (p. 1025, col. 2, where the magnetic particles and the yeast are incubated together for 10 minutes).

With regard to claim 22, Dauer teaches an embodiment of claim 1, which is conducted in the absence of a precipitation or centrifugation procedure (p. 1025, where the magnetic cell

composition is passed through a filter, which is highly magnetized to attract and capture magnetic entities, see p. 1021).

With regard to claim 23, Dauer teaches an embodiment of claim 1, which is conducted in the absence of a poisonous agent (p. 1025, where the magnetic cell composition is passed through a filter, which is highly magnetized to attract and capture magnetic entities, see p. 1021).

With regard to claim 24, Dauer teaches an embodiment of claim l, which is conducted at an ambient temperature ranging from about 0°C to about 35°C without temperature control (p. 1025, col. 1, where the temperature is set at 25 +/- 2oC).

Regarding claim 1, Dauer does not explicitly teach that the cells can be applied to an amplification system.

With regard to claim 1, Grevelding teaches a method comprising d) applying said separated conjugate to a nucleic acid amplification system to amplify a nucleic acid from said target cell or virus, wherein said process does not comprise a step of lysing said target cell or virus to release said nucleic acid prior to applying said separated conjugate to said nucleic acid amplification system (Abstract, p. 4100, col. 1, where the technique of PCR is applied to whole organisms and has been applied to yeast and bacteria).

With regard to claim 2, Grevelding teaches an embodiment of claim 1, wherein the sample is a clinical sample comprising cells from the organism (p. 4100, col. 1, where the cells include S. mansoni, a blood fluke that infects humans).

With regard to claim 3, Grevelding teaches an embodiment of claim 1, wherein the sample is selected from the group consisting of serum, plasma, whole blood, sputum, cerebral spinal fluid, amniotic fluid, urine, gastrointestinal contents, hair, saliva, sweat, gum scrapings,

marrow, tissue and cell culture (p. 4100, col. 1, where the cells include S. mansoni, a blood fluke that infects humans).

With regard to claim 21, Grevelding teaches an embodiment of claim 1, which is conducted in an eppendorf tube (p. 4100, where the process of setting up the reactions occurs in an eppendorf tube).

With regard to claim 25, Grevelding teaches an embodiment of claim 1, wherein the sample volume ranges from about 5 ul to about 50 ul (p. 4100, col. 2, where the reactions were carried out in a total volume of 25 ul).

With regard to claim 28, Grevelding teaches an embodiment of claim 1, wherein the nucleic acid amplification system is selected from the group consisting of polymerase chain reaction (PCR), ligase chain reaction (LCR), nucleic acid sequence-based amplification (NASBA), strand displacement amplification (SDA) and transcription-medicated amplification (TMA) (p. 4100, where the amplification was PCR; see legend to Figure 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the method of Dauer to include further analysis of the captured and released cells using PCR amplification as taught by Grevelding to arrive at the claimed invention with a reasonable expectation for success. As taught by Grevelding, "recently protocols were introduced that allow PCR amplification without DNA extraction" and "we show that PCR amplification is possible from whole, undissected larvae and adults of the fruitfly Drosophila melanogaster and the blood fluke, Schistosoma mansoni without preceeding DNA isolation." While Grevelding teaches isolation from whole organisms, the technique of amplification directly from cells without prior DNA extraction is clearly supported by the

teachings of Grevelding. Therefore, one of ordinary skill in the art would have been motivated to have adjusted the method of Dauer to include further analysis of the captured and released cells using PCR amplification as taught by Grevelding to arrive at the claimed invention with a reasonable expectation for success

Claims 5 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dauer in view of Grevelding as applied to claims 1-4, 6-9, 12-13, 18, 20-25 and 28 above, and further in view of Lopez-Sabater et al. (Letters in Applied Microbiology, 1997, vol. 24, p. 101-104). Dauer teaches a method of isolating cells using magnetic particles (Abstract).

Dauer in view of Grevelding teaches all of the limitations of claims 1-4, 6-7, 12-13, 18, 20-25 and 28 as recited in the 103 rejection stated above. However, Dauer does not teach removing cells suspected of containing a virus before contacting the sample with microbeads. Lopez-Sabater teaches a method for the magnetic immunoseparation for detection of viral sequences by PCR (Abstract).

With regard to claim 5, Lopez-Sabater teaches an embodiment of claim 1, wherein the target virus is an eucaryotic cell virus or a bacteriophage (p. 102, col. 1, where the cells were innoculated with virus and the cells are eucaryotic and therefore the target virus is a eucaryotic cell virus).

With regard to claim 29, Lopez-Sabater teaches an embodiment of claim 1, which further comprises removing cells from a sample containing or suspected of containing a target virus or bacteriophage before contacting the sample with a magnetic microbead (p. 102, col. 1, 'recovery'

heading, where the oyster cells were diced and homogenized, therefore the cells were removed before contacting with a magnetic microbead).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have applied the technique of homogenization of a sample suspected of containing a virus as taught by Lopez-Sabater to the method of isolation and analysis taught by Dauer to arrive at the claimed invention with a reasonable expectation for success. As taught by Lopez-Sabater, "samples (20g) of shucked American oyster… were inoculated with levels of HAV ranging from 10 to 10^3 pfu" and "after 1 hour at room temperature, artificially contaminated oysters were diced with sterile scissors" and subsequently homogenized (p. 102, col. 1). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have applied the technique of homogenization of a sample suspected of containing a virus as taught by Lopez-Sabater to the method of isolation and analysis taught by Dzieglewska to arrive at the claimed invention with a reasonable expectation for success.

Claim 10 is rejected under 35 U.S.C. 103(a) as being obvious over Dauer in view of Grevelding as applied to claims 1-4, 6-9, 12-13, 18, 20-25 and 28 and further in view of Ughelstad et al. (WO83/03920; November 1983). Dauer teaches a method of isolating cells using magnetic particles (Abstract).

Regarding magnetic beads, Dauer teaches that the magnetic particles are ferromagnetic. Ughelstad teaches the details of the process of forming magnetic particles (Abstract).

With regard to claim 10, Ughelstad teaches an embodiment of claim 7, wherein the metal composition is Fe304 (p. 9, where the metal comprises Fe3O4).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have applied the specific teachings of Ughelstad to the particles of Dauer to arrive at the claimed invention with a reasonable expectation for success. As taught by Dauer, "The magnetic seed is a ferromagnetic γ-iron oxide (γ-Fe2O3) or maghemite" (p. 1024, col. 2). Ughelstad teaches wherein the method composition comprises Fe3O4 specifically (see p. 9). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have applied the specific teachings of Ughelstad to the particles of Dzieglewska to arrive at the claimed invention with a reasonable expectation for success.

Claims 11, 19 and 27 are rejected under 35 U.S.C. 103(a) as being obvious over Dauer in view of Grevelding as applied to claims 1-4, 6-9, 12-13, 18, 20-25 and 28 and further in view of Dzieglewska (WO98/51693). Dauer teaches a method of isolating cells using magnetic particles (Abstract).

Regarding claims 11, 19 and 27, Dauer does not teach these specific details regarding the elements of the method as claimed.

With regard to claim 11, Dzieglewska teaches an embodiment of claim 1, wherein the magnetic microbead has a diameter ranging from about 5 to about 50,000 nanometers (p. 9, lines 26-33, where the bead has a diameter of 1-2 um).

With regard to claim 19, Dzieglewska teaches an embodiment of claim 1, which is automated (p. 16, lines 12-14, where the method can be amenable to automation).

With regard to claim 27, Dzieglewska teaches an embodiment of claim 1, wherein the target cell is an epithelia cast-off cell or a bacteria cell isolated from saliva, urine and tissue

culture (p. 5, where the target cell can comprise a bacteria or eukaryotic cell and can be obtained from biological samples including urine).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Dauer to the include elements of Dzieglewska to arrive at the claimed invention with a reasonable expectation for success. As taught by Dzieglewska, "Representative samples thus include whole blood and blood-derived products such as plasma or buffy coat, urine, faeces, cerebrospinal fluid or any other body fluids, tissues, cell cultures, cell suspensions etc., and also environmental samples such as soil, water, or food samples" (p. 5). Dzieglewska also teaches "The invention is advantageously amenable to automation, particularly if particles, and especially, magnetic particles are used as the support" (p. 16). While Dzieglewska teaches a method that comprises lysis of cells prior to amplification, the elements of the claims represented by Dzieglewska are obvious in combination with the teaching of Dauer and Grevelding. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Dauer and Grevelding to the include elements of Dzieglewska to arrive at the claimed invention with a reasonable expectation for success.

Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dauer in view of Grevelding as applied to claims 1-4, 6-9, 12-13, 18, 20-25 and 28 above and further in view of Inuma et al. (Int. J. Cancer, 2000, vol. 89, p. 337-344). Dauer teaches a method of isolating cells using magnetic particles (Abstract).

Dauer in view of Grevelding teaches all of the limitations of claims 1-4, 6-9, 12-13, 18, 20-25 and 28 as recited in the 103 rejection stated above. Neither Dauer nor Grevelding teach that the cells comprise leukocytes. Inuma teaches that leukocytes can be specifically targeted by magnetic beads comprising antibodies (p. 337, col. 2).

With regard to claim 26, Inuma teaches an embodiment of claim 1, wherein the target cell is a leukocyte isolated from whole blood, marrow or lympha (p. 337, col. 2, where 'anti-CD45 Mab-conjugated microbeads... bind to a common antiden of leukocytes').

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have analyzed the target cells of Inuma using the method of separation taught by Dauer to arrive at the claimed invention with a reasonable expectation for success. As taught by Inuma, "prepared cells were resuspended in 80 µl of BSA-PBS mixed with 20 µl of CD45 microbeads for 15 min at 4°C and passed down the MACS column" (p. 338, col. 1). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have analyzed the target cells of Inuma using the method of separation taught by Olsvik to arrive at the claimed invention with a reasonable expectation for success.

Response to Arguments

Applicant's arguments with respect to claims 1-13 and 18-29 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Hardingham et al. (Cancer Research, 1993, vol. 53, p. 3455-3458) teaches a general method for immunobead isolation of circulating tumor cells followed by PCR (Abstract).

No claims are allowed. All claims stand rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEPHANIE K. MUMMERT whose telephone number is (571)272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephanie K. Mummert/
Patent Examiner, Art Unit 1637